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## **Treatment of Senile Hypertension The Fosinopril in Old Patients Study (FOPS)**

Vetter, W

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# Treatment of Senile Hypertension The Fosinopril in Old Patients Study (FOPS)

Willi Vetter

Data regarding the tolerance of ACE inhibitors in old age are sparse, despite this class of compound being regarded as one of the first-line agents for the treatment of hypertension. In the present trial, the efficacy and tolerance of the ACE inhibitor fosinopril was examined over a period of 12 weeks in an open trial of hypertensive patients aged over 60 years with diastolic hypertension (diastolic blood pressure 95 to 110 mm Hg) and isolated systolic hypertension (ISH; systolic blood pressure 160 to 219 mm Hg, diastolic blood pressure 80 to 94 mm Hg). Fosinopril decreased blood pressure from 174/101 mm Hg to 149/88 mm Hg in patients with diastolic hypertension and from 182/86 mm Hg to 151/80 mm Hg in patients with ISH. Seventy percent of patients did not require any adaptation of the initial fosinopril dose to achieve an adequate therapeutic response. In the patients in

whom 20 mg fosinopril did not adequately reduce blood pressure, the addition of 12.5 mg hydrochlorothiazide was found to be slightly more effective than doubling the initial dose of the ACE inhibitor. Fosinopril was well tolerated and the occurrence of drug-dependent side effects was not increased in patients with renal insufficiency. Fosinopril is an excellent therapy for the treatment of hypertension in elderly patients, particularly because, as a consequence of its dual, compensatory excretion, no adaptation of the dose is necessary, even in patients with a physiological reduction in renal function. *Am J Hypertens* 1997; 10:255S-261S © 1997 American Journal of Hypertension, Ltd.

**KEY WORDS:** Hypertension, fosinopril, elderly patients, angiotensin converting enzyme inhibitors.

**T**he prevalence of hypertension in the elderly in the Western world is clearly on the increase, currently reaching a figure of 35% to 45%.<sup>1-3</sup> Apart from the total increase in subjects aged >65 years, a number of additional factors are responsible for the growth of the elderly hypertensive population, particularly the problem of definition and the specific metabolic features associated with old age.<sup>4</sup> Hypertension in the elderly also presents particular problems in terms of diagnosis. Because of the reduced compliance of arterial vessels

observed in old age, systolic blood pressure is often underestimated, whereas the diastolic blood pressure is often overestimated.<sup>5,6</sup> Since the middle of the 1980s, the Swiss Association against High Blood Pressure (SVGHBD) has been calling for higher blood pressure limits (> 180/100 mm Hg) as the therapeutic threshold. The generally accepted World Health Organization (WHO) definition of arterial hypertension<sup>7</sup> can only be regarded as conditionally applicable in old age. Screening studies have revealed that increasing age is more and more frequently accompanied by isolated systolic hypertension (ISH; systolic blood pressure  $\geq$  160 mm Hg and diastolic blood pressure < 90 mm Hg).<sup>5,8</sup> Many studies have stressed the need for appropriate treatment of such hypertension to reduce cardiovascular and cerebrovascular risk.<sup>4,9,10</sup> In particular, the incidence of stroke can be reduced by anti-

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hypertensive therapy even in patients aged over 80 years<sup>9</sup> and in addition, the Swedish Trial in Old Patients (STOP) study showed a clear reduction in total mortality of 43% associated with antihypertensive therapy.<sup>11</sup>

Hypertension in the elderly presents particular problems in terms of diagnosis as the reduced compliance of the arterial blood vessels in old age tends to mean that systolic blood pressure is underestimated, whereas diastolic blood pressure is overestimated.<sup>6,10</sup> Older people frequently have a wide range of other medical problems and accordingly take more medicines. This polytherapy can increase the incidence of drug-related side effects, partly because of potential drug interactions, but also because drug accumulation can occur in association with a physiological deterioration in the renal function with age.<sup>11</sup> Recently, however, the European Working Party on High Blood Pressure in the Elderly (EWPHE) Trial noted a very low side effect rate (8%) in elderly patients,<sup>12</sup> and the STOP Trial did not show an increased rate of withdrawal from the trial in the treatment group as compared with the placebo group.<sup>13</sup>

Drug-related adverse events have a major effect on patient compliance. Elderly patients often have a range of comorbid conditions and therefore frequently require a number of different medications. Thus, an increased incidence of side effects would be expected resulting from altered pharmacokinetics, potential drug interactions, and reduced kidney function associated with older age.<sup>12</sup> Until recently, patient compliance in the elderly has been regarded as particularly poor. The Systolic Hypertension in the Elderly Programme (SHEP) and data from our own group has revealed a compliance comparable with that of younger patients in similar circumstances.<sup>14,15</sup> Whether or not elderly patients are less compliant with long-term therapy, it is well established that compliance can be improved by well tolerated medication and by simple medication regimens.<sup>16-18</sup>

The efficacy of ACE inhibitors in elderly patients with hypertension has been satisfactorily demonstrated.<sup>19-21</sup> Very little is known, however, about the tolerability of ACE inhibitors in old age,<sup>19,20</sup> despite the fact that this class of compound must be regarded as first-line agents for the treatment of hypertension in the light of its mechanism of action.

The aim of the Fosinopril in Old Patients Study (FOPS) trial was to examine the efficacy and tolerability of the ACE inhibitor fosinopril in elderly hypertension patients with relatively normal renal history.

## PATIENTS AND METHODS

In this open-label trial, carried out by 241 practicing physicians in Switzerland, hypertensive men and women aged 60 years or over were treated with fosi-

**TABLE 1. ADMISSION AND EXCLUSION CRITERIA IN THE FOSINOPRIL IN OLD PATIENTS (FOPS) TRIAL**

Admission criteria
Age $\geq 60$ years
Informed consent
Group 1: Diastolic blood pressure 95–110 mm Hg
Group 2: Diastolic blood pressure 80–94 mm Hg
Systolic blood pressure 160–219 mm Hg
Exclusion criteria
Age $< 60$ years
Diastolic blood pressure $> 110$ mm Hg
Systolic blood pressure $\geq 220$ mm Hg
Inadequately controlled Diabetes mellitus
Serum creatinine $> 180 \mu\text{mol/L}$
An established exclusion criterion for administration of an ACE inhibitor

nopril. The inclusion and exclusion criteria are shown in Table 1. The patient population was divided into two groups on the basis of their hypertension: Group 1 with an increased diastolic blood pressure (95 to 110 mm Hg), and Group 2 with ISH (diastolic blood pressure 80 to 94 mm Hg; systolic blood pressure 160 to 219 mm Hg) (Table 1).

At admission, subjects underwent clinical examination and laboratory tests prior to administration of the study medication (20 mg fosinopril once daily in the morning). Follow-up visits were made after 3, 6, and 12 weeks (the conclusion of the trial), during which laboratory analyses and assessment of the efficacy and tolerability were performed. During the third visit (week 6) the fosinopril dose could be doubled if necessary, or supplemented with 12.5 mg hydrochlorothiazide (HCTZ), to achieve better blood pressure control. This was recommended if the systolic blood pressure remained  $> 160$  mm Hg and the diastolic blood pressure remained  $> 90$  mm Hg.

The creatinine clearance in relation to sex, weight, and serum creatinine was calculated by means of the Cockcroft and Gault formula.<sup>22</sup> Three prospectively defined groups were formed on the basis of the calculated creatinine clearance: normal renal function (creatinine clearance  $\geq 80$  mL/min); slight impairment of renal function (creatinine clearance  $\geq 50$  and  $< 80$  mL/min); and moderate or worse renal insufficiency ( $< 50$  mL/min).

The efficacy of fosinopril, the need for an increase in medication, and the nature and frequency of side effects and their correlation with the degree of renal function was analyzed on an "intention-to-treat" basis. Statistical evaluation of the results was carried out by an external institute (Brunner & Hess, Software, Zürich), using the SPSS Programme. The Wilcoxon

TABLE 2. DEMOGRAPHICS OF PATIENTS COMPLETING FOPS

	Group 1		Group 2		Total
	Women	Men	Women	Men	
No. of subjects	331	201	60	36	628
Age (years; mean $\pm$ SD)	69.7 ( $\pm$ 9)	67.1 ( $\pm$ 10)	73.7 ( $\pm$ 7)	69.6 ( $\pm$ 9)	62.9 ( $\pm$ 9)
BMI* (kg/m <sup>2</sup> )	27.3	27.6	26.5	26.5	27.2
BMI* < 27.3 kg/m <sup>2</sup> (%)	59	59	59	64	59
BMI* $\geq$ 27.3 kg/m <sup>2</sup> (%)	41	41	41	36	41
Systolic BP (mm Hg)	175	172	182	182	175
Diastolic BP (mm Hg)	101	101	86	86	98
Serum creatinine ( $\mu$ mol/L)	91	101	92	99	—
Creatinine clearance (mL/min)	61	76	56	69	66
Blood potassium (mmol/L)	4.32	4.44	4.34	4.29	4.36
Total cholesterol (mmol/L)	6.45	6.07	6.16	6.00	6.27
Triglycerides (mmol/L)	1.80	1.94	1.69	1.86	1.84
No. of patients receiving previous treatment	190	92	30	19	331
Concomitant conditions	176	110	34	18	338
None (%)	46.8	45.3	43.3	50.0	46.2
Diabetes mellitus (%)	4.5	10.4	5.0	5.6	6.5
Lipid disorders (%)	4.5	6.0	6.7	0.0	6.5
Obesity (%)	68.5	8.0	3.3	2.8	7.5
Cardiac symptoms (%)	6.6	6.5	13.3	11.1	7.6

\* BMI, body mass index.

test and the Student *t* test were used for assessing the variation in the mean blood pressure.

## RESULTS

**Patients** A total of 757 patients were enrolled in the trial: 649 (85.7%) in Group 1 (diastolic hypertension) and 108 (14.3%) in Group 2 (ISH). Sixty-three percent

of the participants were female. The demographics of the patient groups are shown in Table 2. A total of 532 (82%) patients in Group 1 and 96 (89%) patients in Group 2 completed the full 12 weeks of the trial; 75 patients withdrew from the trial as a result of side effects, 28% because of inadequate compliance, and the remainder for other reasons.

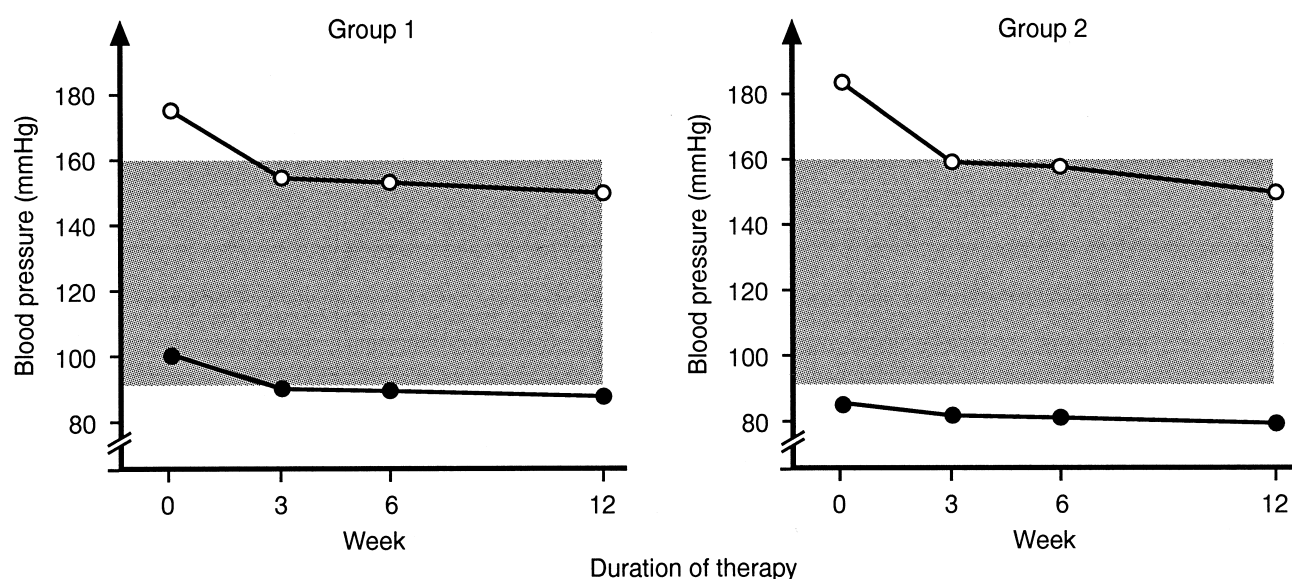
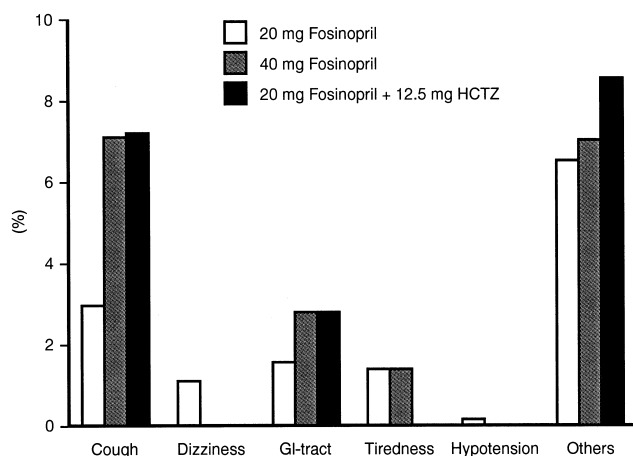


FIGURE 1. Blood pressure response in patients on fosinopril by group. (Group 1: DBP  $\leq$  90 mm Hg; Group 2: SBP  $\leq$  160 mm Hg).



**FIGURE 2.** Nature and frequency of reported side effects as a function of treatment regimen.

**Efficacy** A good antihypertensive response to fosinopril was obtained in Group 1, with reduction in the blood pressure from 174/101 mm Hg to 149/88 mm Hg after 12 weeks (Figure 1). The greatest reduction in blood pressure, both systolic and diastolic, was achieved during the first 3 weeks. In Group 2, a marked reduction in systolic blood pressure was obtained, whereas the decrease in diastolic blood pressure was not statistically significant (182/86 mm Hg *v* 151/80 mm Hg) (Figure 1).

It was not necessary to increase the initial dose of fosinopril (20 mg once daily) in 70% of the patients. After 12 weeks, blood pressure reached normal values in 82% of patients in Group 1 and 84% of the patients in Group 2. Fifty-two percent of the patients in Group 1 and 64% of the patients in Group 2 had a normalization of blood pressure following an increase in the initial fosinopril dose (to 40 mg once daily) and 68% and 67% of patients, respectively, had a normalization of blood pressure following supplementation with 12.5 mg HCTZ. All decreases in blood pressure values from baseline were statistically significant, with the exception of the decrease in diastolic blood pressure in patients with ISH receiving fosinopril 40 mg/day or fosinopril in combination with HCTZ.

**Side Effects** A total of 219 incidences of side effects were recorded in 149 of 757 patients (19.7%) during the observation period (Figure 2). The incidences of side effects were 19.0% in Group 1 and 24.1% in Group 2, and women reported side effects more frequently than did men (22.4% *v* 15.1%). In both groups, cough was the most frequently reported side effect (6.3% and 6.5% in Group 1 and Group 2, respectively), followed by gastrointestinal complaints (4.9% *v* 8.5%) and dizziness (2.2% *v* 3.7%). In addition, increased fatigue was reported in 5.6% of the patients in Group 2. Hypotension was reported only four times (0.6%) in Group 1 and was not reported in Group 2. A slightly higher side effect rate was reported when the fosinopril dose was increased from 20 mg to 40 mg (14.3% *v* 10.5%), as well as in patients treated with fosinopril/HCTZ (15.9%) (Figure 2).

Seventy-five patients (54 women and 21 men) withdrew from treatment as a result of the occurrence of 126 (97 in women, 29 in men) side effects during the trial. Coughing and gastrointestinal complaints were the most frequently reported events.

**Renal Dysfunction** The demographics of the patients divided into three groups by their calculated creatinine clearance values are shown in Table 3. More than three-quarters of the patients included in the trial, with no history of renal disease, were found to have at least a minor reduction in renal function. Astonishingly, the side effect rates in all three renal functional groups were virtually identical, and no correlation was found during treatment between the frequency of side effects and the degree of reduction of renal function. As is evident in Table 3, only gastrointestinal symptoms and fatigue/weakness were reported more often with increasing impairment of renal function; however, this was not statistically significant. The proportion of patients aged  $\geq 70$  years and the proportion of women were highest in the group with low creatinine clearance.

## DISCUSSION

The aim of the FOPS study was to investigate the efficacy and tolerability of fosinopril in elderly hyper-

**TABLE 3. PRINCIPAL CLINICAL DATA BY CREATININE CLEARANCE VALUES**

Creatinine Clearance	<50 mL/min	50–79 mL/min	$\geq 80$ mL/min
Patients (%)	24	54	22
Mean creatinine clearance (mL/min)	40.0	63.7	96.5
Sex (male/women; %)	21/79	35/65	63/37
GI side effects (%)	8.8	5.8	2.4
Fatigue/weakness (%)	3.3	1.0	0.5

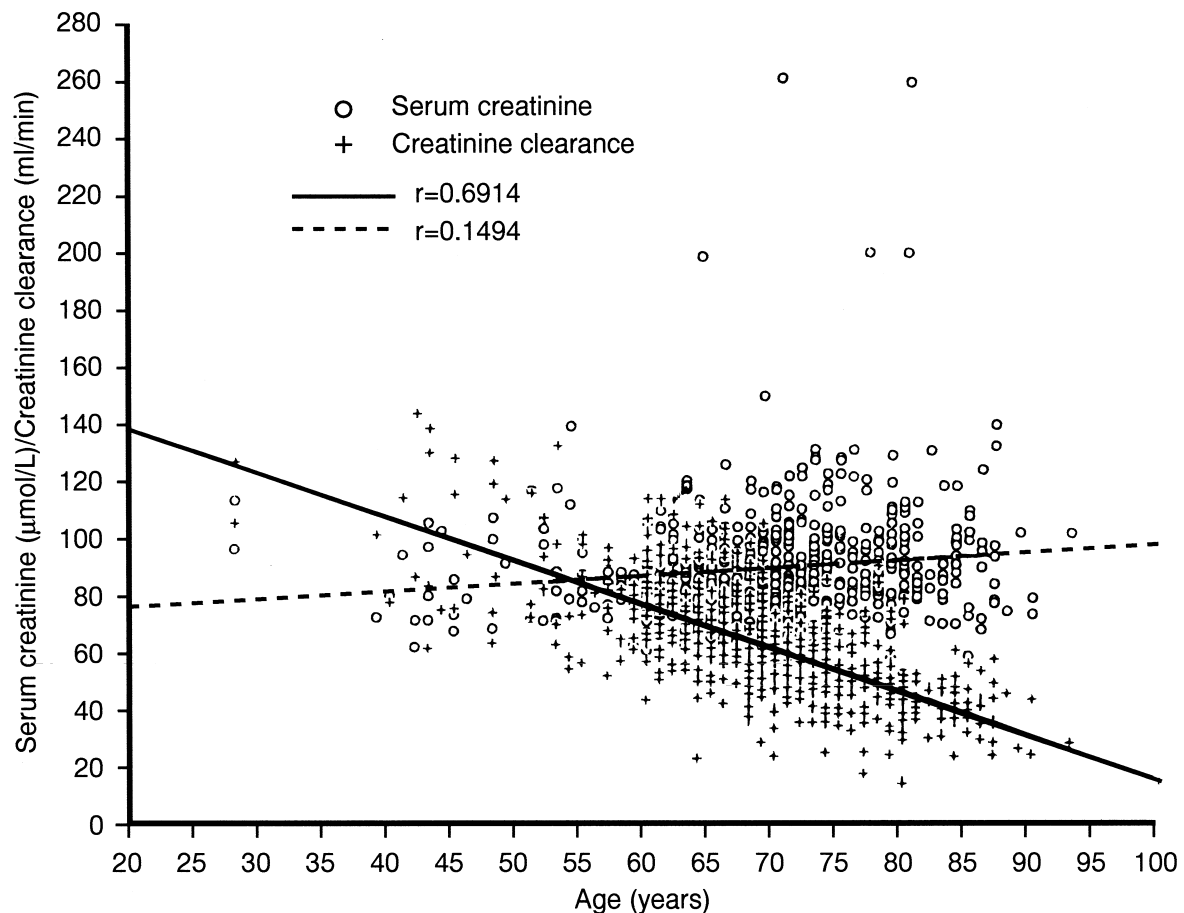


FIGURE 3. Comparison of serum creatinine with creatinine clearance.

tensives without a history of renal disease. The initial dose of 20 mg of fosinopril was sufficient to achieve a normal blood pressure in two-thirds of the patients after 3 weeks, without additional modification of the therapeutic regimen throughout the remainder of the study period. The antihypertensive efficacy of fosinopril was good in older patients with both diastolic and systolic hypertension, with the reduction in blood pressure comparable to that of diuretics or  $\beta$ -blockers.<sup>4,11</sup> The ACE inhibitor/diuretic combination was slightly more effective than was 40 mg of fosinopril, a finding that has already been reported in the literature.<sup>23</sup> In view of the stimulation of the renin-angiotensin-aldosterone system by the diuretic, combination with an ACE inhibitor has a synergistic effect, with the increased renin production from the juxtaglomerular apparatus providing the ACE inhibitor with more substrate.

Fosinopril was well tolerated, and its side effect profile, as shown in Figure 2, largely corresponded to that previously reported. As described in the literature, cough was the most frequent side effect<sup>24,25</sup> and was also the most frequent cause of withdrawal from the trial. This finding again indicates that this side

effect is group-specific,<sup>26,27</sup> even though cough may be less likely to occur with fosinopril than with other ACE inhibitors.<sup>24,25</sup>

In contrast to data in the literature,<sup>28</sup> very few cases of hypotension were recorded in this trial, although the chosen starting was relatively high (in general, treatment initiation with a starting dose of 10 mg is recommended as it has been shown to be an effective dose).

In FOPS, the reduction in creatinine clearance with increased age was very apparent (Figure 3). In the present trial, only 25% of the patients aged >60 years had a normal creatinine clearance. Attention should again be drawn to the discrepancy between serum creatinine and creatinine clearance that is due to the smaller muscle volume in older patients.<sup>29</sup> The physiological reduction of renal function in old age is, however, subject to marked intersubject variability, making it impossible to generally predict the time at which dose adjustment may be necessary for any medication.

The reduced renal function in old age is of particular importance in connection with ACE inhibitors.<sup>30</sup> ACE inhibitors are, in general, excreted via the kid-

neys, mainly from the tubules in the form of acids.<sup>31,32</sup> If renal function is reduced, there is a risk of accumulation of the active agent and an increase in the blood pressure reduction as well as an increased frequency of drug-related side effects.<sup>33-38</sup> In contrast to other ACE inhibitors currently available, fosinopril has a unique pattern of excretion. After ingestion, fosinopril is rapidly converted into fosinoprilat or its conjugated glucuronide, which are excreted via the kidneys or in the bile. In a patient with normal renal function, approximately 50% of fosinoprilat is excreted by the kidney and 50% by the liver.<sup>39</sup> When the excretion capacity of the kidneys or of the liver is reduced, the other organ compensates with increased excretion.<sup>40,41</sup> Therefore, there is risk of drug accumulation only when both organs have a substantially restricted function.<sup>42,43</sup>

There was no difference in either the side effect rate or the withdrawal rate from the trial among groups with creatinine clearance rates of <50, 50 to 79, and  $\geq 80$  mL/min. Only gastrointestinal side effects and fatigue/weakness showed a tendency to increase with deterioration in renal function. It is important to note, however, that the proportion of women and of patients >75 years old, both of which are populations known to have increased side effect rates, were over-represented in the low creatinine clearance group. In addition, there was a lack of dose-dependency in treatment discontinuation. Therefore, fosinopril's compensatory dual excretion mechanism prevented accumulation of the compound, even in patients with medium to severe renal insufficiency. This is of particular advantage in older patients, in whom reduced renal function is frequently undiagnosed, particularly as "normal" serum creatinine level may not reflect normal creatinine clearance.

In this unselected, Swiss population of hypertensive patients aged  $\geq 60$  years, with no prior history of renal disease, at least minor renal insufficiency was found to be present in approximately 75% of patients. The efficacy of fosinopril in a relatively high initial dose of 20 mg once daily was found to be good both in patients with diastolic hypertension and in those with ISH. When increased medication was required to control blood pressure, the results showed that combination with a diuretic was slightly more effective than was doubling the fosinopril dose. The compensatory, dual excretion mechanism of fosinopril appears to be advantageous in daily practice, because the physiological reduction in the renal function with age did not necessitate any adjustment of the fosinopril dose, nor did it lead to a greater incidence of side effects.

To verify the findings of this trial, it would be desirable to undertake a direct comparison of fosinopril

with an ACE inhibitor excreted exclusively via the renal route.

## SUMMARY

It was only at the beginning of the 1990s that the need for considering antihypertensive treatment in many elderly patients was recognized. A consistent means of reducing blood pressure in elderly patients is desirable, in order to prevent cardiovascular accidents. In the present trial, the efficacy and tolerability of the ACE inhibitor fosinopril was examined over a period of 12 weeks, in an unselected outpatient trial in hypertensive patients aged  $\geq 60$  years. Subjects with diastolic hypertension (diastolic blood pressure 95 to 110 mm Hg) and ISH (systolic blood pressure  $\geq 160$  to 219 mm Hg, diastolic blood pressure 80 to 94 mm Hg) were examined separately. Blood pressure was normalized in more than 80% of patients in both groups. If the initial response was inadequate, the addition of 12.5 mg hydrochlorothiazide was found to be slightly more effective than was doubling the initial dose of the ACE inhibitor.

The occurrence of side effects was minimal and was not related to creatinine clearance. The compensatory dual excretion mechanism of fosinopril was of importance, as no adjustment of the dose was necessary even in patients with reduced renal function.

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